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The effect of in-hospital acquired thrombocytopenia on the outcome of patients with acute coronary syndromes: a systematic review and meta-analysis

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Abstract

Background—In-hospital acquired thrombocytopenia (TP) is relatively common among patients hospitalized with acute coronary syndromes (ACS). However, its effect on short-term and long-term outcomes has yet to be reviewed systematically.

Methods—We conducted a systematic review and meta-analysis of clinical studies assessing the relationship between new-onset in-hospital TP and adverse outcomes among ACS patients. MEDLINE, Scopus and the Cochrane Library were searched for eligible studies published before March 20 2016.

Results—Ten studies reporting on a total of 142,161 ACS patients were identified. 8,133 patients showed evidence of new-onset TP during the course of their hospitalization. Compared with patients with normal platelet counts, patients with new-onset TP had a prolonged in-hospital stay, significantly higher risk of both short-term mortality (<30 days) (Odds ratio (OR) [95% confidence interval (CI)]: 5.58 [3.63–8.57]) and late death (6 months to 1 year) (OR [95% CI]: 3.45 [2.35–5.07]), as well as a significantly higher risk of major bleeding events in the first 30 days (OR [95% CI]: 6.93 [5.13–9.38]). In addition, risk for other secondary cardiovascular endpoints,

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including recurrent myocardial infarction, stroke, in-hospital heart failure, stent thrombosis and unplanned revascularization was also significantly higher in the TP versus the no TP group.

Conclusions—Development of TP during the in-hospital management of ACS patients is a significant predictor of both short- and long-term adverse events, including mortality. In the light of this evidence, clinicians should be cautious and closely monitor abnormal platelet counts that present early following an ACS.

Graphical Abstract

Keywords

thrombocytopenia; acute coronary syndrome; myocardial infarction; mortality

INTRODUCTION

Platelets play a key role in the pathophysiology of acute coronary syndromes (ACS) and coronary artery disease (CAD).^{1–3} Indeed, platelet physiology is causally involved in ACS of not only atherosclerotic but also non-atherosclerotic origin, such in the case of community-acquired pneumonia-related ACS.^{4,5} As such, antiplatelet therapy is of critical importance in cardiovascular disease. Recently, the use of newer antiplatelet agents in addition to aspirin has significantly improved outcomes of ACS patients with acceptable rates of bleeding adverse events and is now considered standard of care in the management of ACS.⁶ While it is well established that appropriate antiplatelet therapy is associated with improved outcomes in ACS,^{6,7} the presence of thrombocytopenia (TP) has been associated with a higher incidence of early and late complications.^{8,9} TP either precedes ACS or is acquired during hospitalization and subsequent management.^{10,11} In the latter case, TP is usually linked to drug-related adverse events^{12–14} or invasive procedures such as percutaneous coronary intervention (PCI)¹⁵ and coronary artery bypass grafting surgery (CABG).¹⁶ Indeed, a wide spectrum of complications has been described in patients with ACS that develop TP, which range from ischemic to bleeding adverse events.^{8,9} In most cases these data have derived from post-hoc analysis of large and often heterogeneous clinical studies, raising the need for a systematic review of the available literature and a combined assessment of published findings. Our goal in the present study was to systematically review the incidence of TP among ACS patients as well as the associated risk of mortality, major bleeding events and other secondary cardiovascular outcomes compared to ACS patients with normal platelet counts.

METHODS

Search strategy

This meta-analysis has adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses.¹⁷ The Medline (PubMed), Scopus and Cochrane databases were searched for primary research papers, published in any language form up to March 20 2016. The search was performed by 2 independent reviewers (EO, CP) using the following terms in all possible combinations: “thrombocytopenia”, “thrombopenia”, “acute coronary syndrome”, “myocardial infarction”, “unstable angina”. Reference lists of all studies previously identified as having met the inclusion criteria were also manually reviewed for additional relevant publications. Disagreements were resolved by consensus with the addition of a third reviewer (TR).

Definitions

For the purposes of this systematic review, TP was defined as a nadir platelet count of less than $100 \times 10^9/L$. However, in order to account for the large heterogeneity in the criteria used to define TP in the literature, alternative definitions using absolute or combined absolute and relative criteria (e.g. $<100 \times 10^9$ platelets/L or $>50\%$ drop from baseline) were also accepted as long as the platelet cut-off for diagnosis of TP was $150 \times 10^9/L$. On the other hand, studies that included patients with stable CAD undergoing elective PCI or studies that did not exclude baseline TP were excluded.

Data extraction and endpoints

All data were extracted by two independent researchers (EO, TR) and consensus was reached after the involvement of a third investigator (CP). The primary endpoint was all-cause mortality but data on secondary endpoints of interest such as bleeding events, recurrent myocardial infarction/ischemia, unplanned revascularization, stroke, stent thrombosis and heart failure were also extracted. All endpoints were categorized as short- (in-hospital or within 30 days of the event) or long-term (6 months to 1 year after the event). Pertinent clinical data were also extracted.

Quality assessment

The quality of all eligible studies was critically appraised and rated by two reviewers. Risk of bias in the studies was assessed by the Cochrane Collaboration assessment tool for non-randomized studies.¹⁸ In short, the next key domains were assessed: confounding, selection of participants, departure from intended interventions, missing data, measurement of outcomes and selective reporting.

Statistical analysis

Categorical variables were reported as percentages, whereas continuous variables were reported as median and range, unless stated otherwise. For each dichotomous variable-outcome of interest an unadjusted odds ratio (OR) was calculated using the number of cases and total numbers in the TP versus no TP groups in each study. These were either extracted directly from the original studies or were calculated, where possible, using the available

information. In the meta-analyses, pooled ORs and corresponding 95% confidence intervals (CI) were calculated with the random-effects model estimated by the Mantel-Haenszel method. Statistical heterogeneity between studies was assessed with a χ^2 test and the I^2 statistic; $P < .10$ for the χ^2 test or I^2 greater than 50% indicated significant heterogeneity. Publication bias was visually assessed using the funnel plot method but no further testing was performed given the low number of studies (<10 for each endpoint). The meta-analysis was performed using Review Manager (RevMan), version 5.3 software (Nordic Cochrane Centre, the Cochrane Collaboration, 2014).

RESULTS

Characteristics of the included studies

A total of 2581 studies were identified and 10 were found to meet all criteria as summarized in the PRISMA chart (Figure 1).^{8,9,11,19–25} Eligible studies were all retrospective analyses derived from ACS clinical trials, except for the study by Gore et al. that was based on a global registry for acute coronary events.²² A total of 134,028 patients without TP vs. 8,133 with TP were included and the overall risk of bias for the primary endpoint of all-cause mortality was found to be moderate in all studies.

All studies reported on either short- or long-term mortality rates. Six studies examined patients with non-ST-segment elevation ACS (NSTEMI ACS),^{8,9,11,19,21,23} 2 studied patients with ST-segment elevation myocardial infarction (STEMI),^{20,24} while the rest included patients with any type of ACS.^{22,25} In one study TP was defined as a nadir platelet count $<150 \times 10^9/L$ or a $>50\%$ drop from baseline⁹ and in another the cut-off for TP was set at $80 \times 10^9/L$.²⁵ However the rest of the studies met the goal cut-off of $100 \times 10^9 PLT/L$. The incidence of TP ranged from 0.68% to 16.4% (total pooled incidence was 5.72%). The characteristics of the included studies and populations are summarized in Table 1 & Supplementary Table S1.

Patients that developed TP were consistently older than in the no TP group (range of medians: 61–72 versus 57–67). Notably, there was significant variation in the prevalence of traditional cardiovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, smoking etc.) and previous myocardial infarction (MI), PCI or CABG between the included studies. Despite this between-study variability, within most of the included studies the prevalence of traditional CVD risk factors appeared to be balanced between the TP and no TP groups. The percentage of current smokers was lower in the TP group compared to ACS patients without acquired TP in 7 out of 8 studies.^{8,9,11,20,23–25} Finally, patients with TP had a higher frequency of previous myocardial infarction (7 out of 8 studies^{8,9,11,19,21–23}), CABG surgery (6 out of 7 studies^{9,11,19,21–23}) and renal insufficiency (3 out of 3 studies^{9,20,23}) (Table 1). No significant differences were observed between groups with regard to treatment with unfractionated heparin, even though this ranged significantly between studies (39.9% to 100% in the TP group versus 40.3% to 100% in the no TP group). Treatment with LMWH and direct thrombin inhibitors was less frequent among those who developed TP in 5 out of 6^{9,19,22,23,25} and 3 out of 3 studies^{9,19,21} respectively. On the other hand, the percentage of GPIIb/IIIa antagonist and abciximab use was higher in the TP group in 4 out of 6^{9,19,22,25} and 3 out of 3 studies^{8,20,26} respectively. Patients in the

TP group had a higher percentage of in-hospital CABG surgery (4 out of 4 studies^{11,22,24,25}) but comparable rates of in-hospital PCI (Supplementary Table S1). Median length of stay was reported in 5 studies^{8,11,19,20,24} and was consistently higher among patients that developed TP compared to patients without acquired TP (range of median stay: 4.9–12 days versus 3.6–9 days) (Table 2).

The effect of TP on short- and long-term mortality

Short-term mortality rates were reported in 9 studies and there were a total of 4,576 deaths among 134,726 patients.^{8,9,19–25} Visual assessment by the funnel plot method for these 9 studies showed no evidence of asymmetry (Supplementary Figure S1). Acquired TP during the management of ACS was a significant predictor of short-term mortality (OR[95%CI]: 5.58[3.63–8.57]), however there was significant heterogeneity ($I^2=87\%$) (Figure 2a). Further analysis by TP definition was performed as a form of sensitivity analysis. Only studies on NSTEMI ACS patients were selected which also excluded patients with baseline platelet counts below $150 \times 10^9/L$ or CABG-related in-hospital thrombocytopenia^{9,19}. For a cut-off value of $150 \times 10^9/L$ the summary OR for all-cause mortality was 2.78 (95%CI: 2.45–3.16, $I^2=0\%$), whereas for a platelet cut-off of $100 \times 10^9/L$ in the same studies the summary OR increased to 10.04 (95%CI: 8.06–12.50, $I^2=0\%$). On the other hand, an additional analysis of four studies^{8,22–24} that applied a combined definition of absolute or relative TP ($<100 \times 10^9$ platelets/L or $>50\%$ drop compared to baseline) yielded a summary OR of 3.81 (95%CI: 2.57–5.65) with significant heterogeneity ($I^2=73\%$).

In addition to short-term mortality, acquired TP also predicted long-term mortality (OR[95%CI]: 3.45[2.35–5.07], $I^2=45\%$) (Figure 2b).^{9,11,20,21,25} After analysis was restricted to four studies^{9,20,21,25} using a platelet cut-off value of 80 or $100 \times 10^9/L$, no heterogeneity was detected ($I^2=0$) and the association between acquired TP and mortality risk persisted (OR[95%CI]: 2.81[1.95–4.03]).

The effect of TP on major bleeding events

Definition of major bleeding also varied across studies with five studies using the GUSTO definition for moderate (requiring blood transfusion but not causing hemodynamic compromise) or severe bleeding (intracranial or causing severe hemodynamic compromise),^{8,11,20,21,25} four studies using other composite definitions^{9,19,22,27} and one study using a bleeding index to estimate blood loss.²⁴ Irrespective of the definition used, acquired TP following management for an acute coronary syndrome is associated with a higher risk of major bleeding events (OR[95%CI]: 6.93[5.13–9.38], $I^2=88\%$) (Figure 2c). Further analysis of two studies^{9,19} with a cut-off value of 150×10^9 platelets/L resulted in a summary OR of 3.28 (95%CI: 3.05–3.52, $I^2=0\%$), whereas meta-analysis of 4 studies^{8,19–21} with a cut-off of 100×10^9 platelets/L yielded an OR of 8.72 (95%CI: 6.30–12.06, $I^2=70\%$). Further analysis of three^{8,20,21} of these four studies that used the GUSTO criteria for moderate and severe bleeding resulted in a summary OR of 7.51 (95%CI: 3.79–14.86, $I^2=71\%$).

TP and other cardiovascular endpoints

Interestingly, in-hospital TP is a significant predictor of several adverse outcomes in the first month following an ACS event (Figure 3), predicting a composite endpoint of ischemic and hemorrhagic stroke events (OR[95%CI]: 3.93[1.86–8.32]),^{8,19,20,25} recurrent infarction or ischemia both in the short-term (OR[95%CI]: 2.33[1.94–2.79])^{8,9,19,20,23–25} and in the long-term (OR[95%CI]: 1.64[1.29–2.08])^{9,20,25} and unplanned revascularization procedures (OR[95%CI]: 2.37[1.98–2.83]).^{8,9,20,23} Finally, in-hospital rates of heart failure (OR[95%CI]: 3.37[2.52–4.51])^{19,24} and stent thrombosis (OR[95%CI]: 2.06[1.15–3.69])^{9,20} were also significantly higher in the TP versus no TP group.

Assessing for confounding

Despite the predictive value of in-hospital TP for a variety of outcomes ranging from bleeding and stroke to death, interpretation of our results is limited by the lack of adjustment for traditional CV risk factors. Confounding variables such as age and other comorbidities might be able to explain the predictive value of TP for such events, however not all studies reported the adjusted hazard or odds ratios for the outcomes of interest and heterogeneity in the definition of TP precluded a pooled analysis of these data. The adjusted mortality risk, reported either as adjusted odds or hazard ratios, is summarized in Supplementary Table S2 together with the variables that were included in each multivariable analysis. For instance, in some studies even nadir platelet counts between 100 and 150 x 10⁹/L were independently associated with higher short-term mortality risk compared to platelet counts >150 x 10⁹/L (OR[95%CI]: 2.01[1.69–2.38]),¹⁹ while moderate to severe TP (<100 x 10⁹/L or >50% drop from baseline) was also associated with long-term mortality and short-term major bleeding episodes after multivariable adjustment.¹¹

DISCUSSION

The development of TP in the early ACS setting is relatively common and has been associated with increased mortality and higher rates of both hemorrhagic and ischemic complications regardless of its etiology.^{19,22} To our knowledge, this is the first study to systematically review the incidence and predictive value of acquired TP on both short and long-term outcomes in patients treated for ACS.

The incidence of TP in the ACS setting has been reported in different clinical studies and varies according to the definition used. Even in the studies included in our review, incidence of TP ranged from 0.68% to 16.4%, a large variation possibly explained by heterogeneity in the definition of TP and differences in the medical interventions used in each study. As expected, TP incidence was lower (0.68%) when the cut-off for diagnosis of TP was set at 80 x 10⁹ platelets/L²⁵ and greater for higher cut-off values such as 150 x 10⁹ platelets/L (12.9% in the study by Wang et al).¹⁹

The risk for either bleeding or mortality did not seem to differ significantly between studies that used absolute (<100 x 10⁹/L) versus those that used combined criteria (<100 x 10⁹/L or >50% drop from baseline). However, the importance of relative thrombocytopenia in predicting mortality and adverse events following PCI has been documented before.²⁸ On

the other hand, the risk of mortality appeared to be significantly greater when a lower cut-off (100 vs 150×10^9 PLT/L) was used for the diagnosis of TP. Overall, irrespective of the exact definition used, our review supports the notion that even mild in-hospital TP ($<150 \times 10^9$ PLT/L) should trigger an alarm in the management of ACS.

Even though the specific etiology of acquired TP was not reported in 9 out of 10 studies that were eligible for this review, anticoagulant and antiplatelet agents, PCI and CABG have all been associated with TP through different mechanisms.^{11–16} In the only study where the cause of TP was further defined as either HIT, glycoprotein-associated TP (GAT) or TP due to unknown causes, all three were shown to be associated with a higher risk of mortality, bleeding and ischemic events.²² Indeed, several drugs used in the management of ACS have been linked to a decrease in platelet counts. Heparin-induced TP, particularly type-2, is a well-known immunogenic response to heparin that is associated with both hemorrhagic and thrombotic events.²⁹ Even though its incidence among ACS patients is not well-defined,³⁰ some studies have estimated it at only 0.3%.^{12,31} On the other hand, GPIIb/IIIa inhibitors also carry a risk of TP estimated between 0.5% and 5%.^{32,33} Abciximab on the other hand is associated with a form of pseudothrombocytopenia with a more favorable prognosis.³⁴ In addition, thienopyridines such as clopidogrel have been linked to thrombotic thrombocytopenic purpura.³⁵ PCI and CABG may also lead to TP via procedure-related anticoagulation, hemodilution and mechanical platelet consumption.¹⁹

Overall, the results of this systematic review and meta-analysis clearly demonstrate that acquired TP is associated with increased short and long-term mortality (Table 2, Figure 2), as well as hemorrhagic and thrombotic complications (Table 2, Figures 2 & 3) even when adjusted for age, gender and comorbidities (Supplementary Table S2). In addition, our analysis suggests that the risk of death or bleeding seems to be proportional to the degree of TP. Finally, TP is associated with a prolonged in-hospital stay and higher healthcare costs (median \$14,466 versus \$11,629 in the no TP group, $p=0.001$).²⁰

The existence of a direct causative link between TP and increased mortality risk in ACS patients is not entirely clear. Hemorrhagic complications in the ACS setting are well known to be associated with mortality³⁶ and likely have a cause-effect relation with TP, as described for both baseline and acquired TP.^{10,37} On the other hand, bleeding itself can lead to increased platelet consumption and TP.³⁸ Interestingly, withholding appropriate antiplatelet management because of low platelet counts and fear of adverse bleeding events, could result in a higher risk of thrombotic events or recurrent infarction.¹¹ According to another interesting hypothesis, TP promotes the release of immature platelets from the bone marrow, which contain a significant amount of potentially active messenger ribonucleic acid (mRNA) coding for prothrombotic and proinflammatory proteins.^{39–41} This could also explain resistance to antiplatelet therapy and the paradoxical higher risk for thrombotic events in the TP group that was observed in our study. Finally, according to some authors, the presence of TP represents a marker of poor baseline status and increased severity of the acute coronary event, which could also explain the worse prognosis of these patients.¹⁰ This is further supported by our study, since patients with TP appeared to have a higher prevalence of chronic comorbidities (such as renal insufficiency) compared to individuals

without TP, indicating that TP might indeed identify a subgroup of patients with higher than normal risk.

Age is an important confounding factor in the association between TP and adverse events. Aging has been linked to both decreasing platelet counts but also increased platelet reactivity and reduced effectiveness of adenosine diphosphate receptor (ADP) antagonists.^{42,43} Taken together, these findings suggest that in the elderly, lower absolute platelet counts and platelet resistance to antiplatelet therapies may account for the higher rate of both hemorrhagic and thrombotic events. Even though patients that developed new-onset TP tended to be older than in the no-TP group in all of the studies included in the meta-analysis, the association between TP and mortality persisted after adjustment for age and several age-related comorbidities (Supplementary Table S2).^{9,11,19,21,22} This suggests that the relationship between TP and adverse events cannot be fully explained by age-related differences.

Acquired in-hospital TP should also be distinguished from baseline TP in ACS, which has also been shown to predict mortality and adverse events.^{10,37} Baseline TP is less likely to be due to drug-induced effects and usually reflects a combination of multiple chronic comorbidities and advanced age.¹⁰ Separate studies on both baseline and acquired TP have demonstrated no interaction between the type of drug management and the TP-mortality association.^{10,21} This further supports the notion that TP in the ACS setting rather reflects the combined severity of the event and a patient's overall status.¹⁰

Our study has some limitations. All data derived from a post-hoc retrospective analysis of the data collected from the original clinical studies, which in their majority were originally created to test the efficacy and safety of different medical therapies in ACS management. As already discussed, pooled risk calculations were based on crude, unadjusted data, whereas there was also significant heterogeneity between the included studies. Finally, not all studies excluded patients with CABG-related nadir platelet counts.

CONCLUSIONS

In summary, acquired in-hospital TP represents a major risk factor for early and late mortality as well as major bleeding and several cardiovascular adverse events among patients treated for an ACS. In the light of this evidence, clinicians should be cautious and closely monitor abnormal platelet counts that present early following an ACS. However, despite this clear association, evidence on the optimal management of these patients remains relatively weak.^{6,44} Therefore, further studies are required to determine the underlying pathophysiology and causative factors of new-onset TP in the context of ACS and shape evidence-based guidelines on the optimal medical management of these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- In-hospital acquired thrombocytopenia (IATP) is relatively common in ACS patients
- IATP is a significant predictor of both early and late mortality
- IATP is a risk factor for both hemorrhagic and thrombotic adverse events
- Physicians should monitor closely platelet counts in ACS patients
- Further research is needed on the optimal management of ACS patients with IATP

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for literature search and study selection.

Table 1

Basic characteristics and baseline demographics of included studies (TP/no TP)

Author and year	Original study	Study group size	TP incidence (%)	ACS type	TP definition (x10 ⁹ PLT/L)	Follow-up	Age* (y)	Female (%)	HTN (%)	HLD (%)	DM (%)	Current smoker (%)	RI (%)	Prior MI (%)	Prior PCI (%)	Prior CABG (%)
Vora 2014 ¹¹	SYNERGY	7435	10.9%	NSTE	<100 or >50% drop	1 year	71/ 67**	43.2/ 36.1	76.3/ 67.7	56.5/ 58.4	31.7/ 28.5	19.4/ 24.7	-	33.1/ 28.3	24.5/ 20.7	20.9/ 17.4
Caixeta 2011 ⁹	ACUTY	10836	6.8%	NSTE	<150 or >50% drop	30 days, 1 year	67/ 62	23.5/ 32.4	71.1/ 66.4	60.3/ 57.2	27.5/ 26.6	27.4/ 29.8	25.1/ 18.5	36.9/ 31.1	43.5/ 40.5	25.9/ 18.4
Wang 2009 ¹⁹	CRUSADE	36182	13.0%	NSTE	<100	In- hospital	72/ 67***	43.6/ 42	72.5/ 72.4	55.8/ 55.2	36.8/ 33.3	-	-	32.7/ 29	21.2/ 22.6	22.6/ 19.5
Nikolsky 2015 ²⁰	CADILLAC	1975	2.5%	STE	<100	1, 6, 12 months	65/ 59	28/ 27	46/ 47.5	-	26/ 16.1	36/ 43.4	21.7/ 17.9	10/ 13.9	6/ 11.4	-
McClure 1999 ⁸	PURSUIT	9101	7%	NSTE	<100 or >50% drop	30 days	67/ 64	37.9/ 35.4	57.8/ 55.1	-	26.7/ 22.7	20.6/ 28.7	-	37.8/ 32.1	17.4/ 12.3	11.7/ 11.9
Eikelboom 2001 ²¹	OASIS-2	8912	1%	NSTE	<100	6 months	64.8/ 64.6	28.7/ 39.8	54/ 54.3	-	28.7/ 20.9	23/ 22.4	-	42.5/ 38.6	8/ 7.9	13.8/ 12
Gore 2009 ²²	GRACE	52647	1.6%	any	<100 or >50% drop	In- hospital	70.4/ 66	30.3/ 33	62/ 63	-	30.8/ 25	-	-	34/ 30	21/ 18	15.3/ 12
Yeh 2007 ²³	TIMI-11b	3910	1.4%	NSTE	<100 or >50% drop	14 days	70.2/ 64.2	42/ 35	66/ 49	36/ 33	20/ 20	27/ 32	52/ 28	33/ 32	6/ 12	20/ 13
Harrington 1994 ²⁴	TAMI & urokinase	874	16.4%	STE	<100 or >50% drop	In- hospital	61/ 57	30/ 19	49/ 42	19/ 23	16/ 16	55/ 62	-	-	-	-
Scirica 2006 ²⁵	OPUS-TIMI 16	10288	0.7%	any	<80	30 days, 1 year	66/ 61	38.5/ 27.8	47.1/ 43.1	-	20/ 21.1	31.4/ 36.3	-	-	-	-

* median value

** reference group: >150 x 10⁹ PLT/L and < 50% drop from baseline;

*** reference group: >150 x 10⁹ PLT/L

ACS: acute coronary syndrome; BMI: body mass index; CABG: coronary artery bypass grafting surgery; DM: diabetes mellitus; HLD: hyperlipidemia; HTN: hypertension; MI: myocardial infarction; PCI: percutaneous coronary intervention; RI: renal insufficiency; TP: thrombocytopenia

Table 2

Short- and long-term complications, mortality and cardiovascular outcomes (TP/no TP)

Author and year	TP definition (x10 ⁹ PLT/L)	ACS type	Median length of in-hospital stay (days)	Death (%)	Stroke (%)	Short-term				Long-term		
						Recurrent ischemia or MI (%)	Unplanned revascularization (%)	Post-admission HF (%)	Stent thrombosis (%)	Major bleeding (%)	Death (%)	
Vora 2014 ¹¹	<100 or >50% drop	NSTE	7/4 *	-	-	-	-	-	-	28.2/5.43	28.1/6.7	
	<150 or >50% drop			-	-	-	-	-	-	11.2/6.5	11.5/6.5	
Caixeta 2011 ⁹	<100	NSTE		8.3/1.1	-	-	-	-	-	-	9.5/3.56	
	<150		-	3.1/1.1	-	7.5/4.1	5.3/2.4	-	1.6/0.8	14/4.3	6.5/3.4	
Wang 2009 ¹⁹	<100	NSTE	7/4 *	23.4/2.91	0.3/0.22	0.5/0.412	-	5.3/1.8	-	53.3/11.74	-	
	<150			6.9/2.6	0.39/0.2	0.5/0.4	-	2.76/1.7	-	26.7/10.1	-	
Nikolsky 2015 ^{*,** 20}	<100	STE	4.9/3.6	8/1.6	0/0.9	0/0.9	6.1/3.4	-	2/0.9	10/2.7	10/3.9	
McClure 1999 ⁸	<100 or >50% drop	<100	12/8	7.4/3.3	3/0.6	27.2/12.2	22.4/12.8	-	-	55.9/8.3	-	
				8.1/3.4	3.1/0.6	26.7/12.6	22.2/13	-	-	54.8/9.3	-	
Eikelboom 2001 ²¹	<100	NSTE	-	3.4/0.6	-	-	-	-	-	8.05/1.39	11.5/5.7	
Gore 2009 ²²	<100 or >50% drop	any	-	16.2/4.7	2.9/0.7 (hemor- rhagic)	-	-	-	-	12.3/2.3	-	
Yeh 2007 ²³	<100 or >50% drop	NSTE	-	11/2	-	13/5	15/10	-	-	18/3	-	
Harrington 1994 ²⁴	<100 or >50% drop	STE	12/9	16.1/3.3	-	33/18 (recur. Ischemia)	-	38/14	-	-	-	
Scirica 2006 ²⁵	<80	any	-	11.6/1.7	2.9/0.5	12.1/2.8 (MI) and 2.9/1.6 (ischemia)	-	-	-	19/2	15.8/4.9	

ACS: acute coronary syndrome; HF: heart failure; MI: myocardial infarction; (N)STE: (non-)ST-segment elevation; PLT: platelet; TP: thrombocytopenia

* reference group: >150 x10⁹ PLT/L;

** data given for both in-hospital and 30-day outcomes (outcomes at 30 days are presented here)